MS APPEAL BRIEF - PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Jean PLOUET et al.

Serial No. 09/091,561 Appeal No. _____

Filed August 21, 1998 GROUP 1644

ANTI-IDIOTYPIC ANTIBODIES OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND USE THEREOF AS DRUGS

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS:

1. Real Party in Interest

The real party in interest in this appeal is the assignee, CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE of Paris, France.

2. Related Appeals and Interferences

None.

3. Status of Claims

Claims 1-17 have been cancelled. Claims 18-35 are pending in the present application. Claims 18-24 and 31 were withdrawn from consideration by the Examiner as being drawn to non-elected subject matter. The present appeal is taken from the final rejection of pending claims 25-30 and 32-35.

4. Status of Amendments

No amendment to the claims was made after final rejection. A Response after Final Rejection was filed on September 18, 2002, including additional evidence in support of the patentability of the claims on appeal. In the Advisory Action of October 18, 2002, the Examiner indicated that the Response after Final Rejection would be entered for purposes of appeal.

5. Summary of Invention

The attached claims 25-30 and 32-35 reflect the inventors' discovery of admittedly novel and non-obvious anti-idiotypic vascular endothelial growth factor antibodies. Vascular endothelial growth factors (VEGF) are recognized as the main agents or promoters of uncontrolled angiogenesis and neovascularization observed in tumor progression (see specification at page 1, lines 6-18). The term "anti-idiotypic" connotes a second generation antibody: i.e., an antibody raised not against an antigen (in this case VEGF), but rather against an antibody to that antigen. See, e.g., page 8, lines 3-21 of the specification.

VEGF binds to vascular endothelial cells to stimulate angiogenesis and neovascularization. At the time the present application was filed, it had been demonstrated that VEGF binds to two distinct binding sites found on vascular endothelial cells. The VEGF receptors were identified as KDR/flk-1 and flt-1 (as to the KDR/flk-1

binding site, KDR identifies the binding site as found in humans and flk-1 corresponds to the murine homologue). At the time the application was filed, it had been suggested that VEGF and its binding sites may play a role in vascular development and vascular permeability. However, the specific functions of KDR/flt-1 and flk-1 were unknown. Moreover, it was unknown whether it was possible to activate one binding site without activating the other binding site.

In the present invention, Appellants demonstrate that it is possible to produce anti-idiotypic antibodies that are capable of treating pathologies involved in angiogenesis and neovascularization by the selective activation of the KDR/flk-1 receptor (see page 2, line 20 to page 3, line 15). That is, the anti-idiotypic antibodies of the present invention recognize the human KDR receptor or the murine flk-1 receptor, but do not recognize the flt-1 receptor. With the aid of the anti-idiotypic antibodies of the present invention, it has been possible to demonstrate that KDR/flk-1 is a target of pathological angiogenesis.

The present invention further relates to Fab fragments of the VEGF anti-idiotypic antibodies of the present invention. The Fab fragments bind to KDR and flk-1 but not to flt. By binding to KDR and flk-1, the Fab fragments block VEGF from binding to KDR and flk-1 and inhibit the proliferation of endothelial cells (See page 3, lines 1-23).

The invention further relates to complexes and pharmaceutical compositions, characterized in that they contain, as an active substance, at least one anti-idiotypic antibody of the present invention, or at least one Fab fragment thereof.

6. Issues

The sole issue on appeal, as follows is whether claims 25-30 and 32-35 are enabled by the teachings of the present application, under the first paragraph of 35 USC §112.

7. Grouping of Claims

The claims do not stand or fall together. The claims are grouped separately for purposes of the present appeal, as follows:

First, it is believed that claims 25-26, 29-30, 32-33 and 35 are patentable independently of claims 27, 28 and 34. Independent claim 25 is directed to an anti-idiotypic vascular endothelial growth factor antibody. Claim 26 recites further characteristics of the anti-idiotypic antibody of the present invention. Claims 29-30 and 32 are dependent from claim 25. Claim 33 is dependent from claim 26.

Second, it is believed that dependent claims 27-28 and 34 are independently patentable. Each of those claims are directed to Fab fragments. Applicants note that the specification and declarations address the Fab fragments separate from the anti-idiotypic antibodies of the claimed invention. In fact, it is believed that the specification clearly describes the production of Fab fragments (see present specification pg. 9, lines 13-20 and pg. 13, lines 17-20). As a result, it is believed that claims 27-28 and 34 are independently patentable.

8. Arguments

In the final rejection of June 18, 2002 (Paper Number 29) and the Advisory Action of October 18, 2002 (Paper Number 31), the Examiner contends that claims 25-30 and 32-35 are not supported by an enabling disclosure.

The Examiner alleges that the present application would result in a polyclonal antibody and would not result in the claimed antibody. The Examiner contends that for one of ordinary skill in the art to obtain the claimed antibody, the present disclosure would have to describe in great detail additional screening and isolation steps not disclosed in the present application. The Examiner contends that these steps must be set forth in the present application to enable the present invention. The Examiner also alleges that Fab fragments of the anti-idiotypic

antibodies of the claimed invention are not enabled by the present disclosure.

Applicants respectfully submit that the rejection on appeal does not merit affirmance by the Board for the following reasons:

1) While it is correct that the claimed invention covers both polyclonal and monoclonal forms of the claimed antibodies, the uncontroverted evidence of record establishes that the present specification enables one skilled in the art how to make and use the claimed invention in either form;

2) The evidence of record establishes that one of ordinary skill in the art would readily be able to make either polyclonal or monoclonal antibodies according to the invention, given the teaching of the isolated and purified polyclonal antiserum in present specification; and

3) The present specification clearly enables one skilled in the art on how to produce and use the Fab fragments of the claimed invention.

I. The present specification clearly enables one skilled in the art to make and use the claimed antibody.

In the final rejection, the Examiner alleged that the present disclosure does not enable one of ordinary skill in the art to practice the claimed invention without an undue amount of experimentation. The Examiner contends that the present disclosure is only enabling for a polyclonal antiserum. However, the present disclosure is plainly enabling for the claimed antibody.

The claimed invention is directed to anti-idiotypic VEGF antibodies. The claims do not limit the antibody to a polyclonal or a monoclonal antibody. Moreover, the claimed invention does not require that the antibody be isolated or purified to homogeneity. The claimed invention is broadly directed to an antibody which is a ligand of the KDR/flk-1 receptor yet not a ligand of the flt-1 receptor. Such an antibody is admittedly new, useful and non-obvious, as witness the absence of any rejections under 35 USC §§101, 102 or 103.

In the present disclosure, the polyclonal antiserum is further purified to the Ig2 J fraction described in the present specification and discussed in the

declaration by Dr. Plouet filed on March 25, 2002. Although the Ig2 J fraction may include some anti-idiotypic antibodies that bind to both flk and flt, that fraction also clearly contains the Ig2 J claimed antibody.

Moreover, the claimed antibody is present in the Ig2 J fraction at a concentration level at which one of ordinary skill in the art can readily detect the claimed antibody (see Figures A and B submitted with the declaration of Dr. Plouet filed on March 25, 2002). Thus, while the present specification describes the production of the claimed antibodies in a purified polyclonal fraction, the claimed antibody is indisputably present in the polyclonal antiserum described in the present specification.

As discussed below, the evidence of record further demonstrates that it would be a matter of routine experimentation to further isolate and purify the claimed antibody, as well as to produce monoclonal antibodies using conventional techniques; and, in any event, the Examiner has not carried his burden of demonstrating affirmatively why the present disclosure fails to enable the claimed invention.

II. One of ordinary skill in the art would readily be able to make monoclonal antibodies according to the invention, given the teaching of the purified polyclonal fraction in the present specification.

One of ordinary skill in the art would readily be able to make monoclonal antibodies according to the present invention. In particular, one of ordinary skill in the art would already possess the requisite skills and knowledge to conduct the further protocols, screening and isolation steps to that end. The declarations filed on March 25, 2002 by Dr. Plouet, Dr. Fons and Dr. Cazenave confirm this point. However, Appellants note that the Examiner fails to provide any evidence supporting the contrary contention that one of ordinary skill in the art would not be able to produce a monoclonal antibody given the teaching of the polyclonal antiserum.

Appellants believe that the Examiner fails to meet his burden in showing that the claimed invention is not supported by an enabling disclosure. It is a well-founded principle that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. As a matter of law, the express teaching of the patent specification cannot be

controverted by mere speculation and unsupported assertions on the part of an Examiner. As stated by the Court of Customs and Patent Appeals in the case of *In re Dinh-Nguyen and Stanhagen,* 181 USPQ 46 (CCPA 1974):

> Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. 181 USPQ at 47.

Such a standard must be applied with great rigor when the Examiner's conjecture is contrary to the teachings of the specification. When reviewing the Examiner's position on this point, it is apparent that no evidence is adduced that is in any way inconsistent with the teaching of the specification. Moreover, it is noted that the Examiner fails to provide any evidence contesting the statements made in the declaration attesting to the enablement of the claimed invention.

The Examiner further contends that because the claimed antibody is initially present in a polyclonal antiserum, one of ordinary skill in the art would not be able to take advantage of its special properties absent further screening, isolation and purification steps.

In addition, the Examiner alleges that additional process steps are required in light of the immunization

procedure. The Examiner notes that 80% to 85% of the immunized animals produce none of the claimed antibody of the present invention. The Examiner concludes that the production of the claimed antibody comprises a rare event. The Examiner then assumes that any animal that would produce the claimed antibody would produce little of the claimed antibody. The Examiner concludes that this further demonstrates the need for a further purification step.

However, that same data in fact signifies that one of ordinary skill in the art would readily be able to complete any screening, isolation and purification steps as a matter of routine experimentation. Moreover, the procedure for selecting a monoclonal antibody simply requires one to dilute hybridoma cells to obtain clones derived from a single cell. In this respect, no additional purification steps will be necessary because the biological material used will behave as an anti-idiotypic antibody from an immunized rabbit.

Once a positive reaction has been obtained, it means that among the anti-idiotypic antibodies produced by the given animal, at least one B lymphocyte subset synthesizes an antibody of the present specification. It has been shown that the use of a radio receptor assay in

this case predicts that the B lymphocyte subset of interest is healthy enough to secrete a detectable level of antibodies, and that the splenocytes of the animal can be treated with Kohler and Milstein's procedure.

Inside the polyclonal serum, and due to the idiotypic restriction, there is a high percentage of monoclonal antibodies of interest, which explains why it has been possible to obtain the excellent results set forth in the present application.

It will then be just a matter of time and routine experimentation to obtain monoclonal antibodies by a fusion of the splenocytes of the animal with myeloma cells. The hybridoma cells can then be diluted until a single cell is found that secretes the antibody set forth in the present invention.

Hybridoma technology conventionally used to make monoclonal antibodies uses B-lymphocytes from mice. Given the discovery of the claimed antibody in the polyclonal sera of 15-20% of immunized rabbits, one skilled in the art of anti-idiotypic immunology would expect that a comparable percentage of mice would produce the claimed antibody. See the March 25, 2002 declarations of Plouet, Fons and

Cazenave. In light of the screening methods set forth in the present specification, an analysis of the specificity of mice antibodies by the radio receptor assay would involve only routine experimentation to isolate antibodies of the present invention. For example, when one skilled in the art wants to prepare such monoclonal antibodies, he would have only to follow the procedure descried by Kohler and Milstein to screen mouse or rat sera or hybridoma secretion for the ability to bind flk-1.

Thus, Appellants submit that any additional process steps not recited in the present disclosure would be well known to one of ordinary skill in the art and reflect conventional hybridoma techniques. It is believed that the declarations by Dr. Plouet, Dr. Fons and Dr. Cazenave demonstrate that obtaining such a monoclonal antibody as claimed is simply a matter of routine experimentation, given the teachings of the specification in combination with the level of ordinary skill in the art.

III. The present specification clearly enables one skilled in the art to produce or use Fab fragments of the claimed invention.

Applicants respectfully submit that the Fab fragments of the claimed invention are enabled by the present disclosure. As noted in the declaration by Dr. Plouet filed

on March 25, 2002, the Fab fragments of the present invention are ligands for the flk-1 receptor and not the flt-1 receptor.

Appellants agree with the Examiner in that the Fab fragments of the present invention do not exert the same functional activities of an antibody such as dimerization, internalization and self-proliferation. However, the claims do not recite these functions. The claimed Fab fragment of the present invention is capable of binding to the KDR/flk-1 receptor and not to the flt-1 receptor.

Moreover, applicants note that the specification describes a process for producing the Fab fragments beginning on page 9. The specification teaches that the Fab fragments may be prepared from an Ig2 Id fraction (see present specification pg. 9, lines 13-20 and pg. 13, lines 17-20). The Fab fragments are then chromatographed and recovered.

Thus, Appellants believe that the Fab fragments satisfy the recitations of the claims and are enabled by the present disclosure.

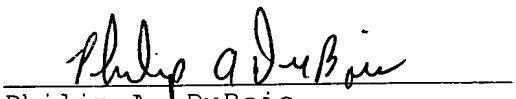
Consequently, the rejection of claims 25-30 and 32-35 as being based on a non-enabling disclosure must be reversed.

9. Conclusion

From the foregoing, it is believed to be apparent that none of the rejections on appeal merit affirmance by the Board, but instead must be reversed. Such action is respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

By 

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10. Appendix

The claims on appeal:

25. Anti-idiotypic vascular endothelial growth factor antibody, said antibody being a ligand of the human KDR receptor or of the murine flk-1 receptor and not a ligand of flt.

26. Anti-idiotypic vascular endothelial growth factory antibody, having the following properties:

a) it targets angiogenic endothelial cells,

b) it is circulating,

c) it has a half-life of about 23 days,

d) it induces phosphorylation on a tyrosine of a protein of 200 kDa,

e) it induces proliferation of vascular endothelial cells,

f) it does not induce migration of endothelial cells,

g) it stimulates angiogenesis,

h) it does not cause arterial hypotension, and

i) it does not affect the permeability of vessels.

27. Fab fragment of the anti-idiotypic antibody according to claim 25.

28. Fab fragment of the anti-idiotypic antibody according to claim 26.

29. Complex between an anti-idiotypic antibody according to claim 25 and a toxin, or between an anti-idiotypic antibody according to claim 25 and a radioactive element.

30. Anti-idiotypic antibody according to claim 25 produced by the following steps:

a) purified VEGF is injected into an animal,

b) blood is withdrawn to recover purified Ig containing specific anti-VEGF IgG, and then in an optional stage the specific anti-VEGF IgG are purified from the purified Ig,

c) said purified Ig or said purified anti-VEGF IgG are injected into an animal of the same origin as that used for injection of the VEGF,

d) blood is withdrawn to recover the total Ig, and then to subject the total Ig to two immunoadsorptions:

(i) an immunoadsorption on an affinity column prepared with the pre-immune Ig of the animal which has been used to produce the anti-VEGF IgG, to eliminate the anti-allotypic or isotypic antibodies,

(ii) an immunoadsorption on an affinity column prepared with the anti-VEGF IgG, to purify the anti-idiotypes.

32. Pharmaceutical composition, comprising an anti-idiotypic antibody according to claim 25.

33. Pharmaceutical composition, comprising an anti-idiotypic antibody according to claim 26.

34. Pharmaceutical composition, comprising the Fab fragment according to claim 27.

35. Pharmaceutical composition, comprising the complex according to claim 29.